REMARKS

Claims 1-32 are pending in the instant application. Claims 1-22 and 13-32 have been rejected. Claim 12 has been objected to but acknowledged to allowable over the prior art. Claims 1, 10, 12, 23, 26, 27, 28, 29, 30, 31 and 32 have been amended. Claims 13-22 have been canceled. No new matter is added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Objection to Claims 24 and 25

Claims 24 and 25 have been objected to as the line numbering was inadvertently copied into these claims during amendment. It is respectfully pointed out, however, that these claims have been canceled. Withdrawal of this objection is therefore respectfully requested.

II. Objection to Disclosure

The disclosure has been objected to as the Examiner suggests that the amendments to the specification which refer to SEQ ID NO:73 of Figure 3 and SEQ ID NO:74 of Figure 5 are confusing because Figures 3 and 5 do not contain SEQ ID NO:73 and 74.

Applicants respectfully disagree since these Figures clearly show the nucleotides C and A positioned above the mismatch nucleotides T and T, respectively, and thus provide a clear teaching of the sequences of SEQ ID NO:73 and 74. Further, Applicants amended the Figure descriptions in the amendment filed July 20, 2004, to include specific reference to SEQ ID NO:73 and 74.

However, in an earnest effort to advance the prosecution of this case, and in accordance with the Examiner's request, Applicants have amended the specification to delete reference to Figure 3 and 5 when referring to SEQ ID NO:73 and 74.

Withdrawal of this objection is therefore respectfully requested.

III. Objection under 35 U.S.C. 132(a)

The Examiner suggests that amendment of the specification to change recitation of "Quantity One" to --QUALITY ONE-- constitutes new matter. Accordingly, Applicants have amended the specification to state --QUANTITY ONE--.

Withdrawal of this objection is therefore respectfully requested.

IV. Rejection of Claims 1-7, 16-22 and 26-32 under 35 U.S.C. 112, second paragraph

Claims 1-7, 16-22 and 26-32 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular the Examiner suggests that claims 1-7 are indefinite in the recitation of predicts "a relatively high level of expression" and predicts "a relatively low level of expression". The Examiner suggests that the terms "high" and "low" are terms of degree and do not make a specific value.

Thus, in an earnest effort to advance the prosecution of this case, Applicants have amended the pending claims in accordance with the Examiner's suggestion to recite a comparison.

Claims 16-19 and claims 26-29 are also suggested to be indefinite over the recitation of "the PCR product" in step (b)(i) of claim 16 and claim 26. This phrase is suggested to lack antecedent basis.

Thus, in an earnest effort to advance the prosecution of this case, Applicants have amended the pending claims in accordance with the Examiner's suggestion to state that "the PCR product produced by amplification with the first and second primer."

Claims 20-22 and claims 30-32 are also suggested to be indefinite over the recitation of "the PCR product" in step (c)(i) because the claims are directed to more than one amplification step and it is unclear which PCR product is being referred to.

Thus, in an earnest effort to advance the prosecution of this case, Applicants have amended the pending claims to state in step (c)(i) that the PCR product is produced by amplification with the second set of primers.

Claims 14-15, 18-19, 21-22, 24-25, 28-29 and 31-32 are also suggested to be indefinite in the recitation of "primer [X or Y] has the sequence corresponding to SEQ ID NO:" because it is unclear if the primer has the sequence of the SEQ ID NO: or not.

Thus, in accordance with the Examiner's suggestion Applicants have amended the pending claims to state "wherein the primer [X or Y] has the sequence of SEQ ID NO: . . ."

Finally, claims 13-32 are suggested to be indefinite in the recitation of "position corresponding to nucleotide 23 of SEQ ID NO:73" or "position corresponding to nucleotide 29 of SEQ ID NO:74" because the claims do not make clear what this position is in reference to.

Thus, in accordance with the Examiner's suggestion, Applicants have amended the claims to state that the position corresponding to

nucleotide 23 of SEQ ID NO:73 is in intron 3 and the position corresponding to nucleotide 29 of SEQ ID NO:74 is in exon 7.

Withdrawal of these rejections under 35 U.S.C. 112, second paragraph is respectfully requested in light of these claim amendments.

V. Rejection of Claims 1, 2 and 5 under 35 U.S.C. 102(a)

Claims 1, 2 and 5 have been rejected under 35 U.S.C. 102(a) as being anticipated by ss903337, September 1, 2000. The Examiner suggests that this reference teaches a sequence which includes a G/A polymorphism as the position corresponding to nucleic acid 23 of SEQ ID NO:73. The Examiner suggests that a method of determining the position corresponding to position 23 of SEQ ID NO:73, as well as a method which includes sequencing a region of the genomic DNA of a subject are inherent in the teachings of ss903337.

Applicants respectfully traverse this rejection.

ss903337 sets forth the sequence for a single nucleotide G/A polymorphism in CYP3A5.

In contrast, claims 1, 2 and 5 of the instant application are drawn to a method for predicting CYP3A5 expression level in a subject based upon determination of the presence of specific CYP3A5

alleles in the genomic DNA of a subject, one of which is a G/A polymorphism at position 23 of SEQ ID NO:73 in intron 7 of CYP3A5.

MPEP 2131 and the case law are clear; a claim is anticipated only if each and every element as set forth in the claim is found either expressly or inherently described in the reference.

There is no express teaching whatsoever in ss903337 regarding significance of this SNP with respect to phenotype of an individual having this SNP. Further, while the Examiner suggests that methods for determining the position of this polymorphism to be at nucleotide 23 of SEQ ID NO:73 and sequencing a region of genomic DNA are inherent in this reference, claims 1, 2 and 5 are not drawn merely to such determinations but rather to the inventive discovery that the presence of an A at the position corresponding to nucleotide 23 of SEQ ID NO:73 on at least one CYP3A5 allele of a subject predicts a relatively high level of expression of CYP3A5 as compared to the presence of a G at that position and the presence of a G at the position corresponding to nucleotide 23 of SEQ ID NO:73 on each CYP3A5 allele of a subject predicts a relatively low level of expression of CYP3A5 as compared to the presence of an A at that position.

Since this claim limitation is neither expressly taught in ss903337 nor inherent, meaning that it necessarily follows by

scientific reasoning from teachings of ss903337, this reference cannot anticipate the invention of claims 1, 2 and 5.

Withdrawal of this rejection under 35 U.S.C. 102(a) is therefore respectfully requested.

VI. Rejection of Claims 1, 2, 5-6, 7-10 and 13-22 under 35 U.S.C. 103(a)

Claims 1, 2, 5, 7-10 and 13-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of ss903337 and Smith et al. (Xenobiotica, vol. 28, pages 1129-1165, 1998).

Claims 6 and 16-22 have also been rejected under 35 U.S.C. 103(a) as being unpatentable over ss903337 and Smith as applied to claims 1, 2, 5, 8-10 and 13-15 above, and further in view of Rootwelt et al.(Human Genetics, vol. 94, pp 235-239, 1994).

Applicants respectfully traverse these rejections.

To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a) three basic criteria must be met. MPEP § 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all of the claim limitations.

The cited combination of references does meet these three basic criteria.

At the outset, it is respectfully pointed out that claims 13-22 have been canceled.

Further, as discussed in Section V, supra, claims 1, 2 and 5, as well as claims 6-7, of the instant application are drawn to a method for predicting CYP3A5 expression level in a subject based upon determination of the presence of specific CYP3A5 alleles in the genomic DNA of a subject, one of which is a G/A polymorphism at position 23 of SEQ ID NO:73 in intron 7 of CYP3A5. Further, claims 8-11 are drawn to a method for determining the cytochrome P450 3A5 (CYP3A5) genotype and phenotype of an individual based upon amplification of specific regions, namely intron 3 and exon 7 of CYP3A5.

Nowhere does the cited combination of references teach or suggest that the presence of an A at the position corresponding to nucleotide 23 of SEQ ID NO:73 on at least one CYP3A5 allele of a subject predicts a relatively high level of expression of CYP3A5 as compared to the presence of a G at that position and the presence

of a G at the position corresponding to nucleotide 23 of SEQ ID NO:73 on each CYP3A5 allele of a subject predicts a relatively low level of expression of CYP3A5 as compared to the presence of an A at that position. Nor does the cited combination of references teach or suggest that the polymorphisms in intron 3 and/or exon 7 of CYP3A5 allele will alter the CYP3A5 phenotype of a individual.

Instead, ss903337 merely sets forth the sequence for a single nucleotide G/A polymorphism in CYP3A5.

Smith et al. provides a general teaching of methodologies for detecting polymorphisms in genes encoding cytochrome P450 enzymes. No teaching or suggestion whatsoever of the G/A polymorphism at position 23 of SEQ ID NO:73 in intron 3 nor its significance with respect to CYP3A5 expression levels and/or the phenotype of an individual is provided by this reference.

Rootwelt et al. is also cited for its general teaching of a method for detecting a G/A polymorphism. However, this reference is not related in anyway to the specific G/A polymorphism at position 23 of SEQ ID NO:73 in intron 3 or its significance with respect to CYP3A5 expression levels and/or the CYP3A5 phenotype of an individual.

Thus, this cited combination of references fails to provide the requisite teaching or suggestion to motivate one skilled in the

art to arrive at the instant claimed invention, namely methods for predicting CYP3A5 expression and CYP3A5 phenotype. Further, this combination fails to provide any reasonable expectation of success with respect to development of methods for predicting CYP3A5 expression levels and determining the cytochrome P450 3A5 (CYP3A5) phenotype of an individual based upon detection of a G/A polymorphism in CYP3A5 and/or amplification of intron 3 or exon 7 of the CYP3A5 gene. Finally, the prior art does not teach or suggest all of the claim limitations since there is no teaching or suggestion of a method for predicting CYP3A5 expression levels or determining the cytochrome P450 3A5 (CYP3A5) phenotype of an individual based upon detection of a polymorphism in intron 3 or exon 7 of CYP3A5.

Withdrawal of this rejection under 35 U.S.C. 103(a) is therefore respectfully requested.

VII. Rejection of Claims 8-9, 11, 13-15 and 23-25 under 35 U.S.C. 103(a)

Claims 8-9, 11, 13-15 and 23-25 have been rejected under 35 U.S.C. 103(a) as being unpatentable over the combination Genbank Accession No. AC005020 (March 21, 2000) and Smith. The Examiner

suggests that the claims are interpreted broadly to encompass sequencing of the CYP3A5 gene. Further, the Examiner suggests that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to sequence the CYP3A5 gene for the purpose of analyzing the sequence to determine if any mutations are present that would be responsible for inter-individual variation in the CYP3A5 gene, as taught by Smith. The Examiner suggests that the ordinary artisan would have been motivated to sequence and analyze the CYP3A5 gene to determine if any variations existed because Smith teaches that inter-individual P450 expression can have profound clinical consequences with regard to pharmacological responses to prescribed medications and that variation between individuals can influence disease susceptibility.

Applicants respectfully traverse these rejections.

The basic criteria for establishing a *prima facie* case of obviousness under 35 U.S.C. 103(a) are set forth in Section VI, supra.

The cited combination of references does meet these three basic criteria.

At the outset, it is respectfully pointed out that claims 13-15 and 24-25 have been canceled. Claim 23 has been amended in accordance with the Examiner's suggestion to state that primer X

has the sequence of SEQ ID NO: 24, or a fragment thereof which is at least ten bases long, and primer Y has the sequence of SEQ ID NO: 25, or a fragment thereof which is at least ten bases long; or that primer X has the sequence of SEQ ID NO: 26, or a fragment thereof which is at least ten bases long, and primer Y has the sequence of SEQ ID NO: 27, or a fragment thereof which is at least ten bases long.

Further, as discussed in Section VI, supra, claims 8-11 are drawn to a method for determining the cytochrome P450 3A5 (CYP3A5) genotype and phenotype of an individual based upon amplification of specific regions, namely intron 3 and exon 7 of CYP3A5.

Nowhere does the cited combination of references teach or suggest that amplification of these specific regions of the CYP3A5 genome would allow for identification of individuals with an altered CYP3A5 phenotype.

Instead, AC005020 merely sets forth the sequence for CYP3A5.

Smith et al. provides a general teaching of methodologies for detecting polymorphisms in genes encoding cytochrome P450 enzymes. No teaching or suggestion whatsoever with respect to alterations in exon 7 and/or intron 3 and their relationship to the CYP3A5 phenotype of an individual is provided by this reference.

Thus, this cited combination of references fails to provide

the requisite teaching or suggestion to motivate one skilled in the art to arrive at the instant claimed invention, namely methods for determining CYP3A5 phenotype based upon amplification of intron 3 and exon 7 of the CYP3A5 gene. Further, this combination fails to provide any reasonable expectation of success with respect to development of methods for determining the cytochrome P450 3A5 (CYP3A5) phenotype of an individual based upon amplification of intron 3 and/or exon 7. Finally, the prior art does not teach or suggest all of the claim limitations since there is no teaching or suggestion of determining the cytochrome P450 3A5 (CYP3A5) phenotype of an individual based upon detection of a polymorphism in intron 3 or exon 7 of CYP3A5.

Withdrawal of this rejection under 35 U.S.C. 103(a) is therefore respectfully requested.

VIII. Allowance of Claim 12

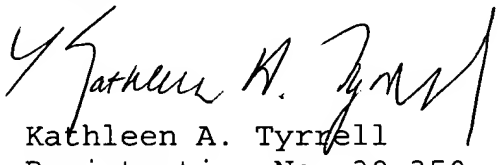
Claim 12 has been indicated to be allowable over the cited prior art but has been objected to as being dependent from a rejected claim. Claim 12 ultimately depends from claim 8. As discussed in detail in Sections VI and VII, claim 8 is also believed to be distinguishable from the cited prior art. Accordingly, amendment of claim 12 to be an independent claim

should not be required for its allowance.

IX. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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